

U.S.S.N. 09/229,226

Filed: January 12, 1999

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

27. (Twice Amended) A method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal using acoustic energy, comprising:

administering acoustic energy at one or more frequencies by applying a transducer to a first site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to alter transport or cell viability at a distant second distant site at [the internal organ,] a different tissue or an internal organ or an internal vessel in a different tissue.

28. (twice Amended) The method of claim 27 wherein the acoustic energy is applied to the skin or a mucosal membrane and alters transport or cell viability at an internal organ, tissue or vessel in a different tissue.

32. (amended) The method of claim [31] 27 wherein the transducer is placed within a blood vessel using a catheter.

33. (amended) The method of claim [31] 27 wherein the transducer is placed within a surgical incision.

**Remarks****Rejection Under 35 U.S.C. § 112, second paragraph**

Claims 1-26 and 31-33 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection if applied to the amended claims 1-33.

Claims 1-26 have been amended to refer to application of the acoustic energy to cells or tissues, and the phrase "biological materials" has been deleted.

U.S.S.N. 09/229,226

Filed: January 12, 1999

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

Claims 27 and 31-33 are not inconsistent. Claim 27 defines a method whether the acoustic energy is applied at a site distant from where efficacy is desired. The acoustic energy does not have to be applied to the skin to be effective at altering permeability or transport at a distant site. For example, it may be useful for targeting a site in the prostate to apply acoustic energy from within the rectum.

**Rejections Under 35 U.S.C. § 102 and 103**

Claims 1, 2, 10, 11, 14, 15, 17, 19, 21, and 23-28 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,113,599 to Klopotek. Claims 27, 28, and 30, were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,445,611 to Eppstein et al. ("Eppstein"). Claim 22 was rejected under U.S.C. § 103(a) as obvious over Klopotek. Claims 1-3, 5, 7, 14, 15, 18, 23, 25 and 26 were rejected under 35 U.S.C. § 103(a) as obvious over Tachibana, et al., Cancer Lett. 72(3):195-199 (1993) in combination with Klopotek. Claims 1-6, 8-18, and 23-26 were rejected under U.S.C. § 103(a) as obvious over U.S. Patent No. 5,636,632 to Bommannan in view of Klopotek. Claims 1-5, 8-18, and 23-26 were rejected under 35 U.S.C. § 103(a) as obvious over Eppstein in combination with Klopotek. Claims 1-5, 8-18, and 23-26 were also rejected under U.S.C. § 103(a) as obvious over Ogden. Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

**Amendments to the Claims**

Claims 1-25 have been amended to depend from claim 27. Claim 26 has been amended to recite the limitation of claim 27 relating to feedback, and application to a first site to have an effect on a second distant site.

U.S.S.N. 09/229,226  
Filed: January 12, 1999  
**AMENDMENT AND RESPONSE TO OFFICE ACTION**

Claims 27 and 28 have been amended to recite that the organ or tissue affected is "*other than*" the tissue to which the ultrasound is applied – i.e., is truly at a distant site in a different tissue, not just a further portion of the tissue to which the ultrasound is applied. Support is found in the application, for example, at page 11, lines 14-20.

Klopotek

Klopotek does not disclose the use of ultrasound to alter transport or cell viability, as defined by claims 27-33, and other claims now dependent thereon. Klopotek is instead related the use of ultrasound to injure connective tissue so that fibroblast cells are activated, so that wrinkles are remodeled. Nowhere in Klopotek is there any mention of altering transport or cell viability, indeed a search of the patent does not identify the terms "transport" or "viability" anywhere in the patent. Indeed, the patent teaches away from transport by virtue of teaching that only ultrasound is required to have the tissue remodel itself, no transport being required, the means being the irritation or stimulation solely by the ultrasound (see col. 3, lines 24-25). The terms "irritation" and "stimulation" are not the same as, nor lead one to, altering cell viability.

Eppstein

Eppstein does not disclose a method for altering cell viability or transport of chemical or biological agents into or through an **internal** organ, **internal** tissue or vessel in a human or other animal using acoustic energy, comprising:

administering acoustic energy at one or more frequencies by applying a transducer to a site on the human or other animal other than where transport or cell viability is to be altered;

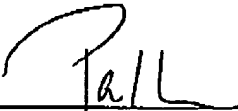
U.S.S.N. 09/229,226  
Filed: January 12, 1999  
**AMENDMENT AND RESPONSE TO OFFICE ACTION**

wherein the acoustic energy is effective to alter transport or cell viability at a **second distant site in a different tissue or an internal organ or internal vessel in a different tissue.**  
(emphasis added)

Eppstein, at most, discloses application of ultrasound which penetrates beyond the epidermis. See, for example, the objects at col. 4, lines 31-37, all of which are to penetrate the stratum corneum. All of the statements in the summary of the invention refer to "transdermal delivery" (col. 4, line 40 to col. 5, line 68). This is not the same as, nor makes obvious, delivery to an internal organ, internal tissue or vessel other than to which the ultrasound is applied.

Allowance of claims 1- 33, as amended, is therefore earnestly solicited.

Respectfully submitted,

  
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U.S.S.N. 09/229,226

Filed: January 12, 1999

MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

**Marked Up Version of Amended Claims**  
**Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)**

1. (twice Amended) [A] The method of claim 27 for treating cells or [biological materials] tissues to alter permeability, cell viability or structural integrity comprising
  - (a) administering acoustic energy to the [biological materials] cells or tissues at one or more frequencies ;
  - (b) measuring a property or the effect of the acoustic energy during the treatment with acoustic energy; and
  - (c) using the measurement obtained in step (b) to modify continued or subsequent application of acoustic energy to the [biological materials] cells or tissues during the treatment as needed to enhance the treatment.
2. (amended) The method of claim 1 wherein the property of the acoustic energy being measured in step b is one or more properties selected from the group consisting of pressure at one or more frequencies, and energy input at one or more frequencies.
3. (twice amended) The method of claim 1 wherein the acoustic energy is effective to alter permeability of the [biological materials] cells or tissues to a chemical or biological agent selected from the group consisting of peptides, proteins, sugars, polysaccharides, nucleotides, polynucleotide molecules, synthetic organic compounds, synthetic inorganic compounds, endogenous organic compounds, endogenous inorganic compounds and combinations and aggregates thereof.

U.S.S.N. 09/229,226

Filed: January 12, 1999

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

4. The method of claim 3 wherein the agent is in a form selected from the group consisting of cells or virus particles, nano or microparticles, liposomes or other lipid vesicles or emulsions.

5. (amended) The method of claim 3 wherein the chemical or biological agent is delivered to cells or [tissue] tissues.

6. The method of claim 3 wherein the chemical or biological agent is detected or quantitated, further comprising  
removing biological fluid or molecules simultaneously, previously, or subsequently to the application of acoustic energy, and  
assaying the biological fluid or molecules to detect or quantitate the chemical or biological agents.

7. The method of claim 1 wherein the acoustic energy is administered to kill cells.

8. (amended) The method of claim 1 wherein the [biological materials] cells or tissues are made more permeable by the exposure to acoustic energy.

9. (twice amended) The method of claim 8 wherein the [biological materials] cells or tissues are made partially or completely reversibly permeable.

10. (amended) The method of claim 1 wherein the [biological materials are] acoustic energy is applied to biological membranes.

11. (amended) The method of claim 1 wherein the [biological material] tissue is skin.

U.S.S.N. 09/229,226

Filed: January 12, 1999

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

12. (amended) The method of claim 1 wherein the acoustic energy is applied to [biological materials] cells or tissue in an amount effective to disaggregate or dissociate the [materials] cells or tissue.
13. (amended) The method of claim 1 wherein the [biological materials are] tissues are blood vessels.
14. The method of claim 1 wherein the acoustic energy is applied at a frequency between 1 kHz and 10 MHz.
15. The method of claim 1 wherein the acoustic energy is ultrasound.
16. The method of claim 1 wherein the acoustic energy is applied at a peak positive pressure of up to 100 atmospheres.
17. (twice amended) The method of claim 1 wherein the acoustic energy is applied under conditions to effect cavitation within or on the surface of the [biological materials] cells or tissues.
18. (amended) The method of claim 1 further comprising administering an agent to enhance transport within or permeability of the [biological materials] cells or tissues.
19. (amended) The method of claim 1 wherein the property of the acoustic energy that is measured is measured at one or more frequencies other than the frequency or frequencies at which the acoustic energy is applied.
20. (amended) The method of claim 1 wherein the property of the acoustic energy that is measured is measured at a frequency or frequencies corresponding to integer multiples of one-half or one-fourth of the frequency applied

U.S.S.N. 09/229,226

Filed: January 12, 1999

## AMENDMENT AND RESPONSE TO OFFICE ACTION

21. (Amended) The method of claim 1 wherein the acoustic energy is measured at one or more frequencies in the acoustic spectrum which do not correspond to peaks in the acoustic spectrum and are taken from the broadband signal of the acoustic spectrum.
22. (Amended) The method of claim 19 wherein the acoustic energy measurement is analyzed using a mathematical algorithm, selected from the group consisting of Fourier Transform and Fast Fourier Transform.
23. The method of claim 1 wherein the application of the acoustic energy is modified by changing an acoustic parameter selected from the group consisting of pressure, energy, frequency, pulse length, total exposure time, duty cycle, and combinations thereof.
24. The method of claim 1 wherein the application of the acoustic energy is modified by changing a non-acoustic parameter selected from the group consisting of temperature, fluid gas content, administration rate of molecules to be transported, sample collection rate, device position, and combinations thereof.
25. The method of claim 1 wherein the application of the acoustic energy input is modified by interrupting the application.
26. (Three times Amended) A device comprising
- (a) means for treating cells or [biological materials] tissue by administering acoustic energy to the cells or [biological materials] tissue at a first site to alter permeability, cell viability or structural integrity of [biological materials] cells or tissues at a second distant site [at one or more frequencies];



U.S.S.N. 09/229,226

Filed: January 12, 1999

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

(b) means for measuring a property or the effect of the acoustic energy during the treatment with acoustic energy; and

(c) means for using the measurement of the property of the acoustic energy to modify continued or subsequent application of acoustic energy to the [biological materials] cells or tissues at the first site during the treatment as needed to enhance the treatment of the cells or tissues at the second distant site.

27. (Twice Amended) A method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or vessel in a human or other animal using acoustic energy, comprising:

administering acoustic energy at one or more frequencies by applying a transducer to a first site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to alter transport or cell viability at a distant second distant site at [the internal organ,] a different tissue or an internal organ or an internal vessel in a different tissue.

28. (twice Amended) The method of claim 27 wherein the acoustic energy is applied to the skin or a mucosal membrane and alters transport or cell viability at an internal organ, tissue or vessel in a different tissue.

29. (Amended) The method of claim 27 wherein the acoustic energy alters transport or cell viability of tumor cells.

U.S.S.N. 09/229,226

Filed: January 12, 1999

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

30. (Amended) The method of claim 27 wherein the acoustic energy alters transport into or out of the cells of molecules selected from the group consisting of therapeutic, prophylactic and diagnostic agents.

31. (amended) The method of claim 27 wherein the transducer is placed inside the body using invasive or minimally invasive means.

32. (amended) The method of claim [31] 27 wherein the transducer is placed within a blood vessel using a catheter.

33. (amended) The method of claim [31] 27 wherein the transducer is placed within a surgical incision.